

Generalised anxiety disorder

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1. Introduction

Generalised anxiety disorder (GAD) is a common disorder with a lifetime prevalence of 6.1% and a 1-year prevalence of 2.9% in one large study.^[1] It occurs most commonly in the 45 - 55-year age group with women twice as likely as men to have GAD.^[1] Although symptoms typically wax and wane in intensity over time, the disorder is characterised by chronicity and is associated with high levels of psychiatric comorbidity (e.g. major depression and other anxiety disorders), physical comorbidity (e.g. gastrointestinal, respiratory, and thyroid disorders) and reduced quality of life.^[2] There have been important advances in the nosology and treatment of this disorder. In particular, there is increasing evidence that patients with GAD and mixed anxiety-depression frequently present in primary care settings,^[3] and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*^[4] provides fairly user-friendly criteria for the diagnosis of GAD. Table 1 lists the diagnostic criteria.^[5]

A few simple points can perhaps be made to help conceptualise GAD. GAD can perhaps be viewed as a 'tension disorder'. This is a useful term in so far as it crosses the boundary between psychic symptoms (worries, feeling 'keyed up', irritability) and somatic complaints (muscle tension, restlessness, insomnia). While GAD patients may not present with 'worries', they often describe themselves as 'worriers' – worry may represent an avoidance behaviour that is used to diminish tension (analogous to the way that agoraphobia may develop after panic attacks).

The algorithm presented here (Fig. 1)^[6] provides a step-by-step approach to the pharmacotherapy of GAD, based on our reading of the research literature. It is important to mention at the outset, however, that psychotherapy approaches may be a first-line intervention in some GAD patients and should be considered in all patients with this disorder. In addition, psycho-education is of the utmost importance, particularly in the initial stages of treatment, and should address the direct effects of anxiety on the life of the patient, as well as possible effects on family members.

2. Diagnosis and clinical characteristics

GAD is characterised by chronic, excessive, difficult-to-control worry and a range of somatic symptoms. Making the correct diagnosis is essential. Given that GAD often presents with somatic symptoms and comorbid psychiatric disorders, the diagnosis is frequently overlooked. It is therefore important to establish (i) that persistent and excessive anxiety and worry about commonly occurring events and activities – on more days than not for at least 6 months – is present; (ii) that difficulty in controlling the worries is concomitant with physical and psychic symptoms; (iii) that the focus of anxiety and worry is not part of another Axis I disorder or due to the direct physiological effects of a substance or a general medical condition; and (iv) that clinically significant distress or functional impairment is evident.^[4]

3. Assessment

Particular attention should be paid to the evaluation of symptoms that are chosen as targets for pharmacotherapy and to symptoms that may point to the presence of other psychiatric disorders. It is also useful to determine the severity of GAD symptoms using a scale such as the Hamilton Anxiety Scale. There are a number of other screening and assessment scales that can be used, including the 7-item GAD scale^[7] for screening for GAD and assessing severity, the Generalized Anxiety Disorder Severity Scale (DGSS) which consists of 8 *DSM-IV-TR* GAD symptoms for the assessment of symptom frequency and intensity^[8] and the Daily Assessment of Symptoms-Anxiety (DAS-A) to assess for symptom improvement.^[9] It is possible that the situation in GAD mirrors that in depression, where less severe forms of the disorder respond equally well to pharmacotherapy and to psychotherapy.

It is also necessary to rule out the presence of comorbid psychiatric and medical disorders. This includes a thorough physical examination, appropriate laboratory investigation (with attention to thyroid and glucose function), and assessment of current use of prescription or over-the-counter medications. Mood disorders, such as depression and dysthymia, other anxiety disorders, and alcohol and other substance use disorders are common in patients with GAD. In addition, attention

Table 1. Criteria for generalised anxiety disorder^{[5]*}

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance)
- B. The person finds it difficult to control the worry
- C. The anxiety and worry are associated with three (or more) of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 months:
 1. Restlessness or feeling keyed up or on edge
 2. Being easily fatigued
 3. Difficulty concentrating or mind going blank
 4. Irritability
 5. Muscle tension
 6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- D. 'The focus of the anxiety and worry is not confined to features of an Axis I disorder
- E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- F. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder

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[†] In the *DSM-V*^[4] this criterion has been changed to: 'The disturbance is not better explained by another mental disorder

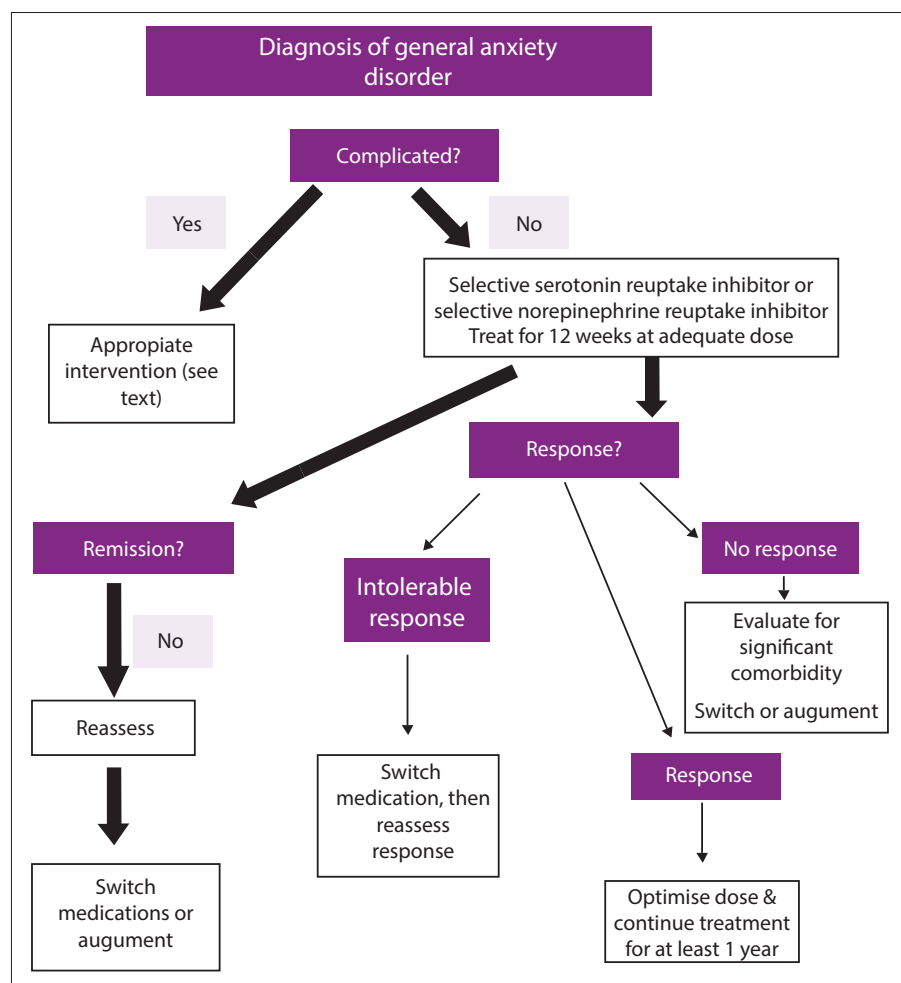


Fig. 1. Algorithm for pharmacotherapy of generalised anxiety disorder.^[6]

should be paid to the possibility of comorbid somatisation disorder. Children with pervasive anxiety probably deserve specialist evaluation before a diagnosis of GAD is made.

4. Treatment

4.1 Treatment goals

The goal of treatment of GAD is reduction and ideally elimination of symptoms or worry and anxiety, and restoration of normal functioning.^[10]

4.2 General aspects of treatment

The initial treatment of GAD can arguably be either medication or psychotherapy as both approaches are efficacious. Several factors may complicate GAD, thus impacting on decisions about the choice of pharmacotherapy and other interventions. The most important factors, along with their treatment implications, are listed below. In addition, prior response to treatment and patient preference are important considerations.

4.2.1 Geriatric patients

Research indicates that GAD in the elderly is not uncommon and is often accompanied by depression.^[11] Given the possibility of accumulation of the drug and consequent adverse effects such as motor vehicle accidents, falls and fractures, benzodiazepines (particularly in high doses or those with long half-lives) should be prescribed only with great caution in this population. In addition, dosages of many other psychotropic medications require adjustment in the elderly.

4.2.2 Alcohol and/or substance use

When the diagnosis of GAD predates the onset of substance abuse, treatment may be initiated relatively soon after abstinence. However, when symptoms of anxiety have their onset during substance abuse or withdrawal, it is likely that a longer period of abstinence is indicated prior to re-evaluation of the need for treatment. In addition, given the risk of dependence, benzodiazepines

should be used with caution in patients with a history of substance abuse.^[12]

4.2.3 Other comorbid disorders

As noted earlier, there is a high rate of comorbidity among GAD, other anxiety disorders and mood disorders. GAD will often respond to the antidepressants that are used as first-line medication in these disorders, and these agents should therefore be considered initially. Similarly, in patients with chronic anxiety and comorbid personality disorder (e.g. borderline personality disorder), antidepressants may be a consideration.

4.2.4 Pregnancy, lactation, menopause

Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. In particular, there is a growing literature pointing toward relative safety of fluoxetine in pregnancy.^[13] Certain benzodiazepines (e.g. chlordiazepoxide) may be safer, while others (e.g. alprazolam) should be avoided during pregnancy and lactation; the lowest effective dose should be prescribed for the shortest possible duration, and high peak concentrations should be avoided by dividing the daily dosage into two or three doses.^[14] Anxiety symptoms may be exacerbated in susceptible patients during menopause, and hormone replacement therapy may be considered as an adjunct to standard pharmacotherapy.

4.2.5 Comorbid medical disorders and medications

Clinicians need to be aware of the multiple interactions between medications used in the treatment of GAD and the treatment of other disorders, as well as of the impact of the medication's adverse effects on medical disorders.

4.3 Pharmacological treatment

The first-line treatment of uncomplicated GAD is a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) drug. Given the substantial comorbidity of GAD with depression and other disorders for which antidepressants are effective, expert consensus favours the use of one of these agents.^[15,16] However, there is evidence for

a range of other agents, including pregabalin, agomelatine, older antidepressants such as tricyclics (TCAs), benzodiazepines, the azapirone buspirone, the antihistamine agent hydroxyzine, the first-generation antipsychotic trifluoperazine and the second-generation antipsychotic quetiapine.^[2,17]

A recent meta-analysis and systematic review of the efficacy of nine drug treatments for GAD notes advantages and disadvantages of several of these agents.^[18] For example, the TCAs (namely imipramine) have been shown effective in GAD in several controlled trials, but are currently considered a second-line option owing to their adverse event burden and toxicity in overdose.^[19] Similarly, given concerns about their tolerability and side-effect profile, caution should be exercised in using atypical and typical antipsychotic medications as monotherapy in GAD.

The benzodiazepines are best reserved for short-term use (2 - 4 weeks) in the early phase of treatment of GAD with an SSRI or SNRI to provide some symptomatic relief until the antidepressant has begun to work, to treat insomnia if it is a predominant symptom, and to protect against occasional early worsening of anxiety seen with the initiation of therapy.^[19] The high comorbidity of symptoms of depression in GAD, and the significant difficulties experienced by many patients during benzodiazepine withdrawal, constitute a strong argument against their long-term use. Benzodiazepines with longer half-lives or slow-release preparations may, however, be associated with fewer withdrawal problems.

Buspirone, a 5-HT_{1A} agonist, takes 2 - 4 weeks or longer to begin working, and appears to be experienced as less helpful in patients recently treated with benzodiazepines.^[20] Its advantage lies in its benign side-effect profile, the lack of dependence, and its proven efficacy in GAD. Disadvantages include a lack of efficacy against the depressive symptoms often found in GAD, and a lack of efficacy in some trials. Whereas some SSRIs have been shown useful in children and adolescents with GAD, a controlled study of buspirone in this population was negative.

Although beta-blockers (e.g. propranolol) are often prescribed by general practitioners for anxiety symptoms, they have unproven efficacy in GAD. Kava extract is a herbal that showed some promise for the treatment of anxiety,^[21] but it has not been studied rigorously enough in GAD, and there are safety concerns, viz. hepatotoxicity.

4.4 Non-pharmacological treatment

Cognitive-behavioural treatment (CBT) has demonstrated efficacy in GAD, where the benefits are maintained at 6 months to 2 years of follow-up.^[22] Treatment of GAD using CBT involves techniques of cognitive restructuring, worry exposure, and behaviour modification. There is currently little evidence that routinely initiating CBT together with medication improves outcome in GAD.

4.5 Acute treatment

The response time to a first-line SSRI (e.g. fluoxetine, citalopram, escitalopram, paroxetine, sertraline) or SNRI (e.g. venlafaxine, duloxetine) is usually between 4 and 12 weeks in GAD, although with adequate dosing a partial response may be evident by 4 - 6 weeks.^[2,23] TCAs and benzodiazepines are also efficacious in the treatment of GAD, but are not considered first-line in view of their adverse event profile (see below). Buspirone is another option in the treatment of GAD (see below).

The first step after drug initiation is to determine response to the medication. This is achieved by careful evaluation of change in symptoms initially targeted for treatment. These are typically excessive worry, various somatic symptoms, and consequent functional impairment. Determining the side-effects of the medication is also important, as these may influence compliance. Patients who are intolerant of a particular medication can of course be switched to another agent or to another class of agents. For example, within the SSRIs, adverse effects may not be seen when an alternative SSRI is used.

When there is a poor response to medication, the first course of action is to optimise dose and duration of the treatment. For many of the antidepressants, there is a relationship between dose and response and also between dose and side-effects. Thus, optimal dosage is as close to maximum recommended doses that the patient can tolerate. Elderly patients generally require lower doses than younger adults. Particularly in the case of the TCAs, clinicians often prescribe suboptimal doses, rather than using doses of 150 mg or more of medications such as imipramine. Even in the case of the SSRIs, some patients may fail to respond to the standard initial starting dose, but do better at higher doses.

Furthermore, there is increasing awareness that some patients may be rapid metabolisers of antidepressant medication and, therefore, require significantly higher doses than usual. When patients on TCAs have little response and few anticholinergic side-effects on average doses of medication (e.g. imipramine 150 mg), it may be useful to further increase dosage with electrocardiogram and perhaps drug level monitoring.

Although benzodiazepines are not recommended as first-line treatments, when used, they should be prescribed in an optimal fashion. In particular, it may be useful to replace short-acting agents with slow-release compounds or long-acting agents. All too frequently, patients on short-acting compounds have intermittent increases of anxiety before the next dose of medication is to be taken.

Buspirone treatment usually begins at 5 mg three times daily. This dose may be increased by 5 mg every 2 - 3 days. Therapeutic doses of buspirone range from 30 mg to 60 mg daily, typically given in divided doses. Buspirone has at least a 2 - 4-week time lag from initiation to clinical onset; optimum duration of a trial of treatment should thus be no less.

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly reassessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.^[24]

4.6 Maintenance treatment

When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite this improvement.^[25] It is recommended that therapy be continued for at least 1 year where there is a good response, given that the disorder is chronic and randomised controlled trials have demonstrated relapse with shorter-term maintenance. It is also important to regularly monitor efficacy and tolerability during long-term treatment. Indeed, guidelines for maintenance therapy of GAD emphasise the safety of modern agents, the likelihood of additional episodes of illness in

patients with repeated past episodes, and the theoretical possibility that appropriate treatment may prevent the onset of secondary disorders.

^[15] Such guidelines have become increasingly conservative, favouring longer courses of medication. When a decision is made to discontinue medication, a gradual taper is recommended (arguably with an even slower taper in the elderly and in medically ill patients).

4.7 Managing partial and non-responders

When GAD does not respond to a clinical trial of adequate dose and duration, it may be useful to reassess a number of important factors that may influence choice of further interventions.

4.7.1 Comorbidity

It is important to establish whether comorbid mood or other anxiety disorders are present. For example, comorbid dysthymia may not respond to buspirone alone, comorbid social anxiety disorder is unlikely to respond to a TCA (other than clomipramine), and comorbid hypochondriasis may require high doses of SSRIs. Excluding important comorbid psychiatric disorders is perhaps the most important step in the evaluation and management of refractory GAD.

4.7.2 Compliance

Many patients with GAD suffer from extreme anxiety and are in fact compliant with their medication. Nevertheless, there is perhaps a tendency for clinicians to overestimate patient compliance. Patients are particularly likely to be concerned about physical or psychological dependence on medication. It is well worth checking not only with the patient, but perhaps also with the family, whether medication is in fact taken as prescribed.

4.7.3 Comorbid substance use

In the presence of active alcohol or substance use, it may be necessary to shift the emphasis of treatment towards a substance use disorder as the primary diagnosis, with the anxiety as a secondary problem. Detoxification is typically a first step in the management of these patients.^[26,27]

4.7.4 Comorbid personality disorders

Although antidepressants may be useful, additional interventions such as psychotherapy may be helpful in patients with chronic anxiety and comorbid personality disorder. While improvement in anxiety symptoms may reduce maladaptive behaviour in patients with comorbid personality disorder, there are other patients (e.g. those with borderline personality disorder) in whom the personality disorder itself may need to be a major target of treatment.

4.7.5 Underlying medical disorder

Patients with GAD who fail to show any noticeable response to treatment should be thoroughly reassessed for the possibility of an underlying medical condition. A range of different medical disorders may lead to chronic anxiety, including endocrine disorders (e.g. hyperthyroidism), respiratory disorders (e.g. chronic obstructive pulmonary disorders), cardiac disorders (e.g. congestive heart failure), and others. If present, such disorders naturally require specific intervention. Note that when using a benzodiazepine in patients

with liver dysfunction, consider using those metabolised only by conjugation (e.g. lorazepam, oxazepam).

4.7.6 Pharmacokinetic issues

Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.

4.7.7 Psychosocial issues

In some cases, a diagnosis of an adjustment disorder with anxious features may be more accurate than that of GAD, and a psychotherapeutic approach therefore indicated. This factor may partially explain high rates of placebo response in some clinical trials in GAD. In other cases of chronic anxiety, psychosocial factors may be enduring and therefore continuously complicate treatment of GAD until given independent attention.

Where there is only a partial response to an initial 12-week trial, it is prudent to re-evaluate the patient and to consider switching to another antidepressant within the same class or to a different class (e.g. SSRI to SNRI or agomelatine, SNRI to SSRI or agomelatine), or augmentation.^[24] Neither augmentation nor switching strategies in GAD have been well researched. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side-effects, drug interactions).^[28] When insomnia is present, the use of an appropriate agent (e.g. non-benzodiazepine gamma-amino-butyric acid (GABA)-ergic hypnotics such as zolpidem, agomelatine, or mirtazapine) may be considered.^[24] If comorbid depression is present, augmentation with bupropion, buspirone, or an atypical antipsychotic may be considered. Similarly, if there is a comorbid bipolar disorder, a mood stabiliser, anticonvulsant or an atypical antipsychotic may be considered. Augmentation with psychotherapy is another important consideration.

5. Summary points

- Both pharmacotherapy and psychotherapy are efficacious first-line approaches for GAD.
- First-line pharmacotherapy of uncomplicated GAD comprises use of an SSRI or SNRI drug.
- A range of other psychotropics are useful for the treatment of GAD.
- Response time to a first-line selective SSRI (e.g. fluoxetine, citalopram, escitalopram, paroxetine, sertraline) or SNRI (e.g. venlafaxine, duloxetine) is usually between 4 and 12 weeks in GAD.
- Benzodiazepines (e.g. lorazepam, alprazolam, diazepam) are best reserved for short-term use (2 - 4 weeks) in the early phase of treatment of GAD with an SSRI or SNRI to provide symptomatic relief.
- Given concerns about their tolerability and side-effect profile, caution should be exercised in using atypical and typical antipsychotic medications as monotherapy in GAD.
- CBT for GAD involves techniques of cognitive restructuring, worry exposure, and behaviour modification.
- Neither augmentation nor switching strategies have been well researched in GAD. Where there is only a partial response to an optimal 12-week trial, consider switching to another antidepressant within the same class or to a different class (e.g. SSRI to SNRI or agomelatine, SNRI to SSRI or agomelatine).

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